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(54) **Use of a potassium channel activator for pharmaceutical compositions useful in cardiopulmonary bypass and organ transplant.**

(57) In accordance with the present invention novel methods for cardiopulmonary bypass and organ transplant, each employing a potassium channel activator, are disclosed. The use of a potassium channel activator has been found to reduce the damage or ischemia induced by the bypass and transplant procedures.

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Cardiopulmonary bypass and heart transplant are two important surgical procedures used by cardiac surgeons. While they both are designed to improve cardiac functional status, the techniques could be greatly improved. In both cases, the procedures require that the hearts be removed from the normal circulation of the body and thus by definition, some degree of damage may be observed. In bypass and transplant, cardioplegic solution, rather than blood, is employed to perfuse the coronary arteries. Accordingly, the conditions and attendant risks/damage resulting from these procedures may differ from coronary stenosis induced damage. To reduce the degree of surgical damage, the hearts are perfused in a retrograde fashion with a cardioplegic solution designed to reduce energy needs of the tissue by arresting the hearts, making them hypothermic (reduce energy demands) and also supplying them with essential substrates. While such solutions are helpful, further improvements in the ability of these hearts to compensate for the surgical damage would be useful. Cardiopulmonary bypass involves aortic cross-clamping and retrograde infusion of cardioplegic solution while heart transplant involves removal of the heart from a donor and the heart is stored in cardioplegic solution or is retrogradely perfused using a Langendorff type system until transplant can be affected.

It has long been known that potassium leaks out of myocardial cells during ischemia and the amount of potassium which leaks out seems to be correlated with the degree of ischemic damage. Indeed, potassium leaks out of hearts subjected to the type of global ischemia which would be seen during cardiopulmonary bypass and heart transplant. Current thinking indicates that compounds which could block the outward flux of potassium, i.e., potassium channel blockers, could protect the ischemic tissue.

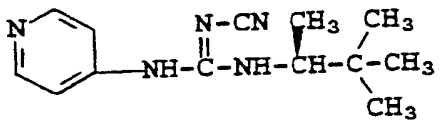
The present invention relates to the use of a potassium channel activator, in the preparation of a pharmaceutical composition useful in reducing the damage or ischemia induced by the bypass and transplant procedures.

The pharmaceutical composition prepared according to the present invention containing a potassium channel activator is added to any solution used to perfuse the coronary arteries or used in connection with bypass and transplant procedures. These solutions may be selected from any of the various cardioplegic solutions, intracellular solutions, etc., which are used to perfuse the arteries, to store the organ, to arrest the heart for transplant, etc. Additionally, the pharmaceutical composition prepared according to the present invention comprising the potassium channel activator may be administered to a mammalian specie, i.e., monkey, dog, cat, rat, human, etc., which is involved in the bypass or transplant procedure. For example, a potassium channel activator can be administered to a bypass patient, organ donor and/or organ recipient before, during and/or after the bypass or transplant procedure.

In a preferred embodiment the present methods involve the use of a potassium channel activator which has little or no vasodilating effect on normal tissue. Such selective compounds have been found to open only the potassium channels in ischemic tissue and therefore pharmaceutical compositions comprising such compounds offer protection of the organ for bypass- or transplant-induced ischemic damage, but have little or no blood pressure lowering activity on the patient.

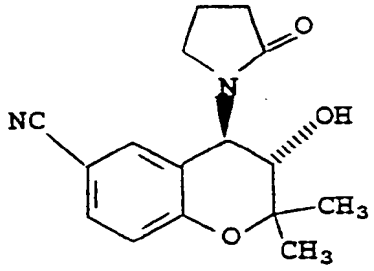
While the use of the pharmaceutical compositions prepared according to the present invention relating to transplant procedures is most frequently described in terms of heart transplant, it is meant to include other types of organ transplant as well. Organ transplant procedures which would also benefit from use of a pharmaceutical composition containing a potassium channel activator, especially the ischemia selective activators, include liver and kidney transplants.

Any potassium channel activator may be used in accordance with the present invention. Suitable potassium channel activators include those disclosed in U. S. Patent 4,057,636, especially the compound

A 

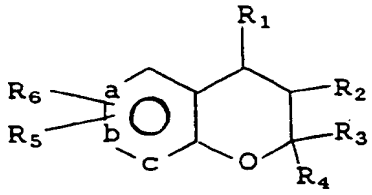
known as pinacidil; those disclosed in European Patent Publication number 0 274 821, especially the compound

B



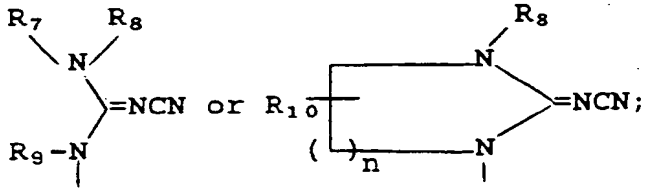
known as cromakalim; nicorandil; minoxidil; compounds in copending application U. S. Ser. No. 506,632 filed April 9, 1990 having the formula

C

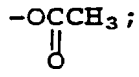


wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

R_1 is

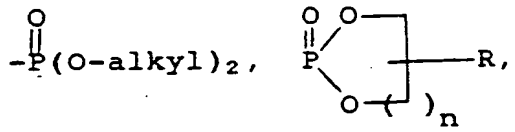


R_2 is hydrogen, hydroxy,



R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, -NO_2, -COR, -COOR, -CONHR, -$CONR_2$, -CF_3, S-alkyl, -SOalkyl, -SO_2alkyl,



halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 and R_8 are each independently selected from hydrogen, alkyl, alkenyl, aryl, (heterocyclo)alkyl,

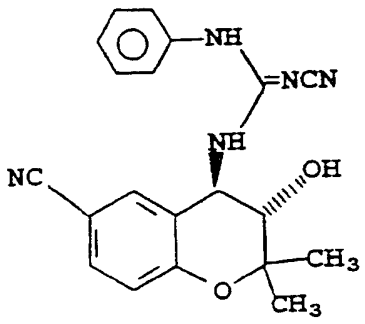
heterocyclo, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R_7 and R_8 taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphilinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and

n is 1, 2 or 3;

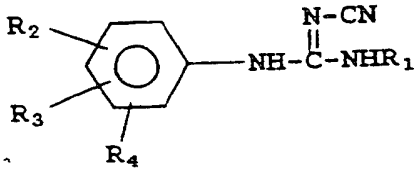
with the compound

C'

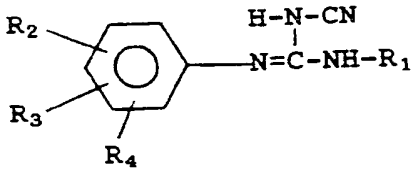


being preferred; compounds in copending application U. S. Ser. No. 349,021 filed May 8, 1989 having the formula

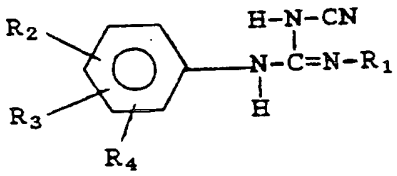
D



and its possible tautomers



and



including pharmaceutically acceptable salts;

wherein R_1 is alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, arylalkyl or cycloalkylalkyl;

R_2 is -C≡N, $-NO_2$,

$-\overset{O}{\overset{\|}{C}}R_5$, $-\overset{O}{\overset{\|}{C}}-OR_5$, $-\overset{O}{\overset{\|}{C}}$-amino,

$-\overset{O}{\overset{\|}{C}}$-substituted amino,

$-CF_3$ or

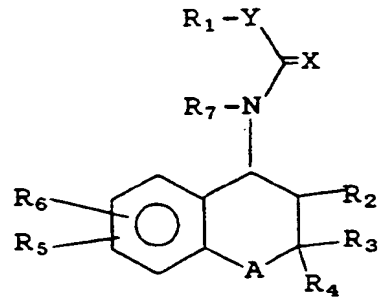
$-\overset{(O)_m}{\overset{\|}{S}}-R_1$;

R_3 and R_4 are each independently selected from $-R_2$, hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, halo, alkoxy, -NHalkly, $-N-(alkyl)_2$, -S-alkyl, -O-arylalkyl, -S-arylalkyl or -S-aryl, -O-aryl, -NHarylalkyl, or R_2 and R_3 taken together are a group which forms a ring with the two carbon atoms to which they are attached, which group is selected from

$-\overset{(O)_m}{\overset{\|}{S}}-(CH_2)_n-CH_2-$,

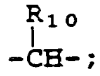
$-\overset{O}{\overset{\|}{C}}X(CH_2)_pCH_2-$, $-\overset{O}{\overset{\|}{C}}-CH_2(CH_2)_pX-$;

wherein
m = 1 or 2,
n = 3-5,
p = 2-4,
X is 0, NR_5, CH_2; and
R_5 is hydrogen or R_1;
compounds in copending application U.S. Serial No. 540,423 filed June 18, 1990 having the general formula

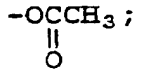


E

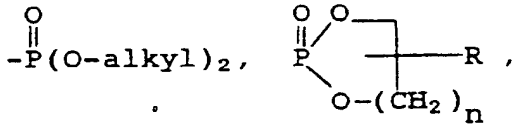
wherein A can be $-CH_2-$, -O-, $-NR_9-$, -S-, -SO- or $-SO_2-$, where R_9 is hydrogen or lower alkyl of 1 to 4 carbons;
wherein X is oxygen or sulfur;
Y is $-NR_8$, -O-, -S- or



R_1 is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl;
R_2 is hydrogen, hydroxy,

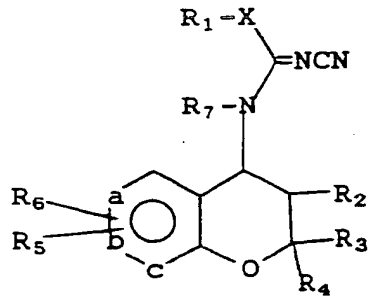


R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;
R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,

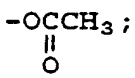


halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;
R_6 is selected from H, alkyl, halo, OH, O-alkyl, amino and substituted amino;
R_7 and R_8 are each independently selected from hydrogen, alkyl, arylalkyl;
n is 1, 2 or 3; and,
R_{10} is hydrogen, hydroxy, alkyl or O-alkyl; and compounds in copending application Serial No. 502,967 filed April 2, 1990 having the general formula

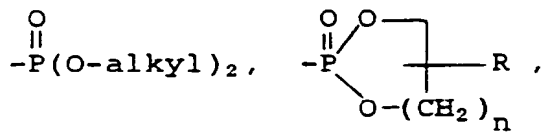
F



wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons; where X is oxygen or sulfur;
R_1 is selected from aryl, arylalkyl, (heterocyclo)alkyl, heterocyclo, cycloalkyl and (cycloalkyl)alkyl.
R_2 is hydrogen, hydroxy,



R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;
R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,



halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 is selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and,

n is 1, 2 or 3.

As discussed above, it has been found that compounds of formula C, E and F are extremely useful and preferably used in the present invention for the preparation of pharmaceuticals useful in bypass and transplant since they have been shown to reduce LDH release in globally ischemic rat hearts while little or no reduction in blood pressure would be expected in whole animals. These and other "ischemia selective" compounds are a class of compounds wherein anti-ischemic effects comparable to the potent vasodilator cromakalim are realized, but with significantly reduced vasodilatory action.

Thus, the most preferred compounds which are those having IC_{50} (rat aorta) values greater than cromakalim (as shown in the examples), i.e. those having the highest degree of selectivity, are compounds of formula C wherein R_7 is aryl, arylalkyl, heteroaryl or heteroarylalkyl; and compounds of formula E and F where R_1 is aryl, arylalkyl, heteroaryl or heteroarylalkyl.

In accordance with the present methods, the pharmaceutical composition comprising the potassium channel activator is added to the cardioplegic solution utilized to perfuse the coronary arteries during bypass, and is added to the cardioplegic solutions for arresting and storage of the heart or other organ for transplant. The pharmaceutical composition comprising a potassium channel activator may be administered to the bypass patient before and/or during and/or after surgery or be administered to recipients and donors before and/or after transplant.

When administered to the mammalian organ donor or recipient or bypass patient, the dosage of the potassium channel activator should be in the range of 1-50 mg/kg. Administration of the pharmaceutical composition comprising the potassium channel activator to donor/recipient can be by any techniques known in the medical arts, e.g., orally, parenterally, intranasally, transdermally and the like, using known pharmaceutically acceptable formulations and delivery systems. This can be accomplished by compounding about 10 to 500 milligrams of a potassium channel activator into a pharmaceutically acceptable carrier by known techinques.

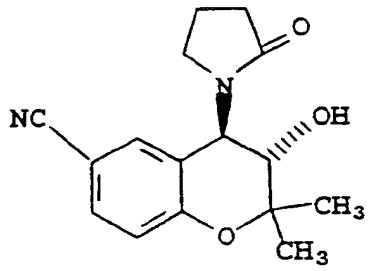
The potassium-channel activator can be present in the cardioplegic solutions in concentrations from about 3 μM to 60 μM and preferably is present in an amount ranging from 7 μM to 30 μM.

Grover et al., "Dissociation of Cardiodepression from Cardioprotection with Calcium Antagonists: Diltiazem Protects Ischemic Rat Myocardium with a Lower Functional Cost as Compared with Verapamil and Nifedipine", Journal of Cardiovascular Pharmacology; pages 331-340, Vol. 14, No. 2 (1989), describe a model for testing globally ischemic, isolated rat hearts. This model is expected to be a reliable indicator of protection since the laboratory-induced isolation and ischemic event including perfusion with a cardioplegic solution, reasonably duplicates the environment and conditions for the heart during bypass and transplant. Grover et al. express the efficacy of protective agents as the amount of lactate dehydrogenase (LDH) release and post-ischemic cardiac function. Lactate dehydrogenase is an enzyme released in the heart during an ischemic event and is an index of cardiac cell necrosis. In the Grover et al. model, this is measured during reperfusion and an agent which provides for lower release levels of LDH is considered to offer greater cardioprotection since lower LDH indicates a smaller infarct size. Cardiac function is determined using the double product (DP) of heart rate times the left ventricular developed pressure (LVDP) divided by 1,000.

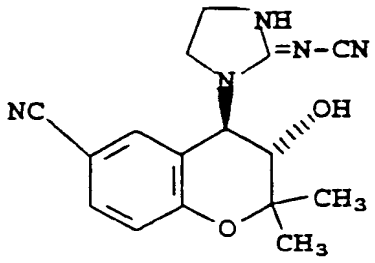
The lower the value for DP before the ischemic isolation of the heart for a given agent, the more cardiodepressant it is considered to be and the higher the value of DP is during reperfusion, the more cardioprotective the agent is.

The following Example examines cromakalim, a potassium channel activator having vasodilator/blood pressure lowering activity, and compounds from formula C, E and F, which have little or no vasodilating activity in normal tissue.

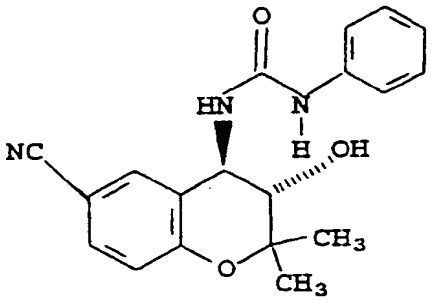
Compounds Tested in the Example



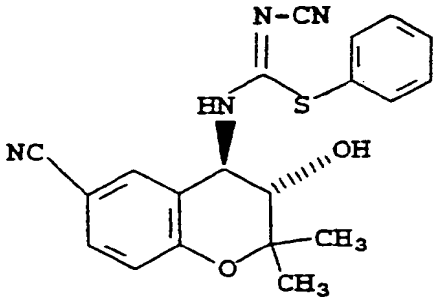
Cromakalim



C"



E"



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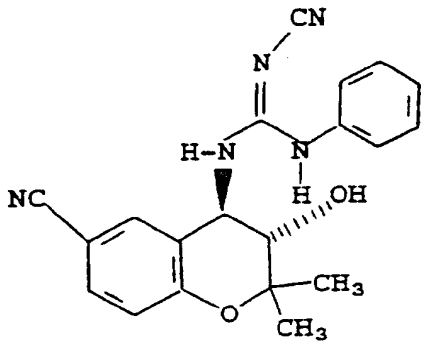
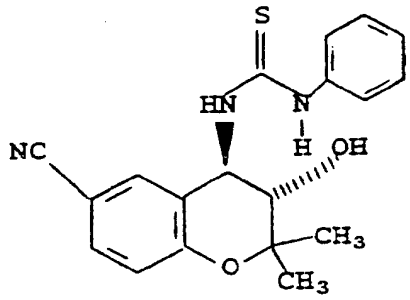
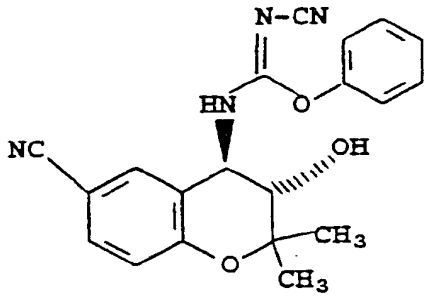


C'



E'



F'

EXAMPLE

Preparation of the Isolated Perfused Hearts

Male Sprague-Dawley rats (450-550 g) were used in all experiments. The rats were anesthetized using

30 mg/kg sodium pentobarbital (i.p.). They were intubated and then treated with i.v. heparin (1000 U/kg). While being mechanically ventilated, their hearts were perfused *in situ* via retrograde cannulation of the aorta. The hearts were then excised and quickly moved to a Langendorff apparatus where they were perfused with Krebs-Henseleit bicarbonate buffer (112 mM $NaCl_2$, 25 mM $NaHCO_3$, 5 mM KCl, 1.2 mM $MgSO_4$, 1 mM KH_2PO_4, 1.25 mM $CaCl_2$, 11.5 mM dextrose, and 2 mM pyruvate bubbled with 95% O_2 - 5% CO_2) at a constant pressure (75 mm Hg). A water filled latex balloon attached to a metal cannula was then inserted into the left ventricle and connected to a Statham pressure transducer for measurement of left ventricular pressure. The hearts were allowed to equilibrate for 15 minutes at which time end diastolic pressure (EDP) was adjusted to 5 mm Hg and this was maintained for 5 minutes. Pre-ischemia or pre-drug function, heart rate and coronary flow (extracorporeal electromagnetic flow probe, Carolina Medical Electronics, King, N.C.) were then measured. Cardiac function was determined using the double product of heart rate (HR) X left ventricular developed pressure (LVDP) divided by 1000. Cardiac temperature was maintained throughout the experiment by submerging the hearts in 37°C buffer which was allowed to accumulate in a stoppered, heated chamber.

Experimental Protocol

Once the baseline measurements were taken, the hearts were treated with 10 μM cromakalim, compounds C', C'', E', E'', F', F'' (n = 4 each) or with vehicle buffer (0.01% DMSO, n = 7). All of these hearts were treated with their respective drugs or vehicle for ten minutes. At this time, post-drug cardiac function and flow were measured and then the hearts were made globally ischemic by shutting off the buffer perfusion. The ischemia was maintained for 25 minutes, the hearts were then reperfused with nondrug treated buffer. Reperfusion was maintained for a total of 30 minutes and at this time reperfusion function and flow were again determined. The results are summarized in the TABLE below.

Also included in the TABLE are the IC_{50}(m) values for rat aorta. The IC_{50} (rat aorta) value is the concentration of the particular compound which inhibits agonist-induced constriction in rat aorta by 50 percent. Thus, the lower values indicate greater vasodilation and it should be noted that these values are for normal, i.e., non-ischemic, tissue. It can be seen that cromakalim with an IC_{50} of 5.7×10^{-8} m is a relatively potent vasodilator in non-ischemic tissue. The ischemia selective compounds, however, are comparable in the anti-ischemic effects (LDH) but have only a fraction of the vasodilator action in non-ischemic tissue.

TABLE

Protective Effect of Potassium Channel Activators

Compound	Pre-ischemic Event (Post Drug) HR	LVDP	DP	FLOW	Ischemic Isolated Rat Heart Reperfusion (Post-Ischemic Event) HR	LVDP	DP	FLOW	LDH	IC_{50}(m) Rat Aorta
Vehicle	245	144	35.5	15.5	186	28	5.6	14.7	21.94	---
Cromakalim	250	131	33.0	23.9	234	87	20.5	13.9	8.89	5.7×10^{-8}
C' (33,812)	244	134	32.7	15.2	244	74	18.2	13.2	10.41	1.37×10^{-6}
C" (34,061)	250	121	29.8	20.4	240	62	14.8	10.1	9.88	4.47×10^{-7}
E' (34,629)	236	141	32.75	15.3	229	55	14.83	13.4	13.46	1.71×10^{-6}
E" (34,628)	234	128	30.06	24.8	230	81	18.52	17.56	8.77	8.05×10^{-7}
F' (34,268)	238	128	30.5	16.0	212	28	6.2	10.4	21.7	$>1 \times 10^{-4}$
F" (34,696)	239	159	38.02	28.3	247	59	14.72	13.92	10.65	4.9×10^{-6}

Concentration: 10 µM
Occlusion: 25 minutes
Reperfusion: 30 minutes

HR = Heart Rate
LVDP = Left Ventricular Developed Pressure (mmHg)
DP = Double Product
LDH = Lactate Dehydrogenase Release

Claims

1. Use of a potassium channel activator for the preparation of a pharmaceutical composition useful in protecting an organ and surrounding cells in a mammalian species subject to an organ surgery procedure.

2. Use according to claim 1 wherein said procedure is cardiopulmonary bypass surgery.

3. Use according to claim 1 wherein said procedure is organ transplant surgery.

4. Use according to claim 3 wherein said procedure is heart transplant surgery.

5. Use according to claim 1 wherein said pharmaceutical composition prepared is added to a solution used in said procedure in order to preserve, protect or maintain organ function.

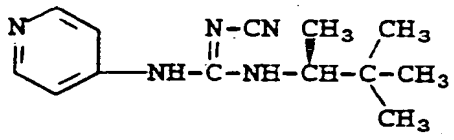
6. Use according to claim 5 wherein said pharmaceutical composition prepared is added to a cardioplegic solution used to arrest, perfuse, store and/or protect a heart involved in a cardiopulmonary bypass or heart transplant procedure.

7. Use according to claim 2 wherein the pharmaceutical composition prepared is administered to a mammalian specie undergoing said bypass procedure before and/or during and/or after said procedure.

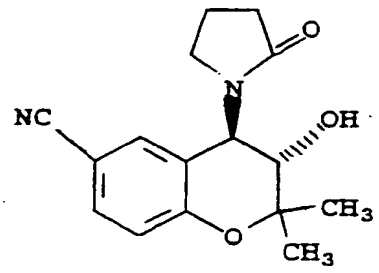
8. Use according to claim 4 wherein the pharmaceutical composition prepared is administered to an organ donor before, during or after removal of said organ from said donor.

9. Use according to claim 4 wherein said pharmaceutical composition is administered to an organ recipient before, during or after transplantation of said organ into said recipient.

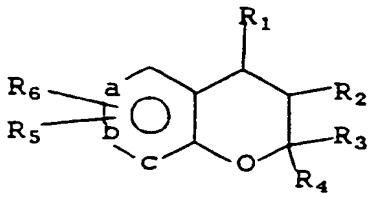
10. Use according to any one of claims 1 to 4 wherein said potassium channel activator is selected from

A 

known as pinacidil; the compound

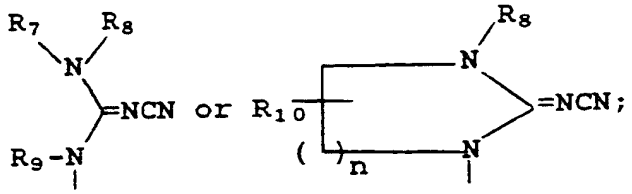
B 

known as cromakalim; nicorandil; minoxidil;
compounds having the formula C

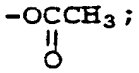
C 

wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

R_1 is

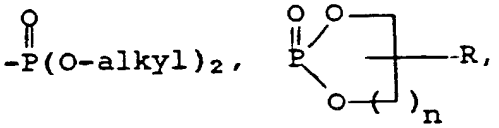


R_2 is hydrogen, hydroxy,



R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,



halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

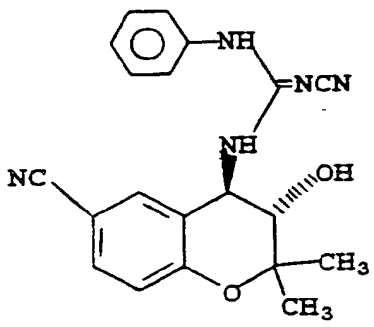
R_7 and R_8 are each independently selected from hydrogen, alkyl, alkenyl, aryl, (heterocyclo)alkyl, heterocyclo, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R_7 and R_8 taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphilinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and

n is 1, 2 or 3;

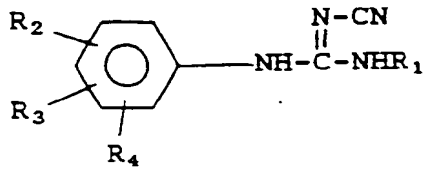
with the compound

C'

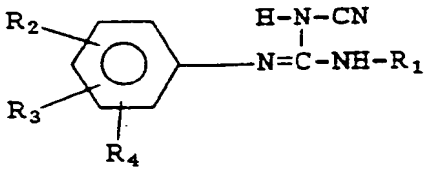


being preferred; compounds having the formula

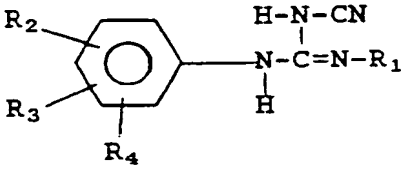
D



and its possible tautomers



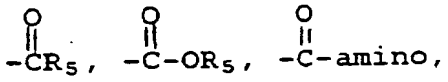
and

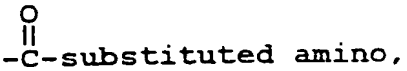


including pharmaceutically acceptable salts;

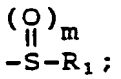
wherein R_1 is alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, arylalkyl or cycloalkylalkyl;

R_2 is -C≡N, $-NO_2$,

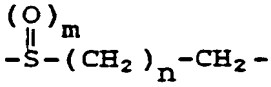


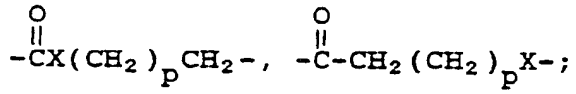


$-CF_3$ or



R_3 and R_4 are each independently selected from $-R_2$, hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, halo, alkoxy, -NHalkyl, $-N-(alkyl)_2$, -S-alkyl, -O-arylalkyl, -S-arylalkyl or -s-aryl, -O-aryl, -NHarylalkyl, or R_2 and R_3 taken together are a group which forms a ring with the two carbon atoms to which they are attached, which group is selected from





wherein

m = 1 or 2,

n = 3-5,

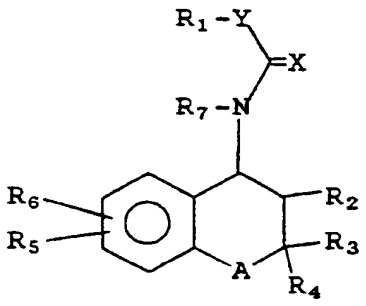
p = 2-4,

X is 0, NR_5, CH_2; and

R_5 is hydrogen or R_1;

compounds having the general formula

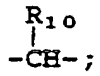
E



wherein A can be $-CH_2-$, -O-, $-NR_9-$, -S-, -SO- or $-SO_2-$, where R_9 is hydrogen or lower alkyl of 1 to 4 carbons;

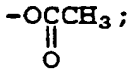
wherein X is oxygen or sulfur;

Y is $-NR_8$, -O-, -S- or



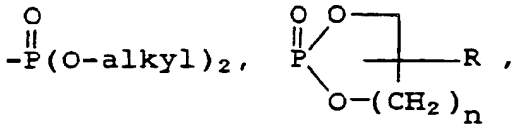
R_1 is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl;

R_2 is hydrogen, hydroxy,



R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,

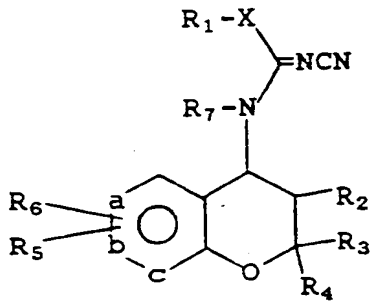


halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

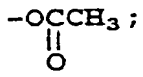
R_6 is selected from H, alkyl, halo, OH, O-alkyl, amino and substituted amino;

R_7 and R_8 are each independently selected from hydrogen, alkyl, arylalkyl;
n is 1, 2 or 3; and,
R_{10} is hydrogen, hydroxy, alkyl or O-alkyl; and compounds having the general formula

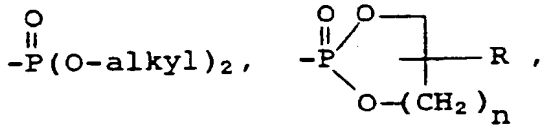
F



wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;
where X is oxygen or sulfur;
R_1 is selected from aryl, arylalkyl, (heterocyclo)alkyl, heterocyclo, cycloalkyl and (cycloalkyl)alkyl.
R_2 is hydrogen, hydroxy,



R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;
R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,

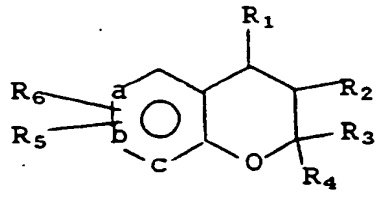


halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;
R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;
R_7 is selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and,
n is 1, 2 or 3.

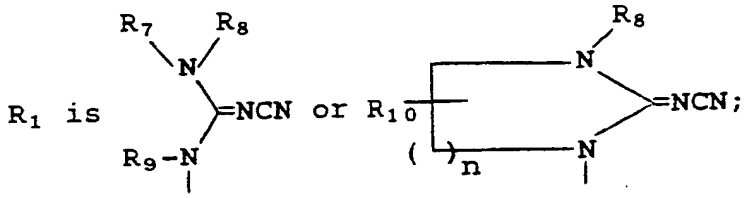
11. Use according to any of claims 1 to 10 wherein said potassium channel activator shows little or no vasodilation activity in normal tissue.

12. The use of claim 11 wherein said potassium channel activator is selected from

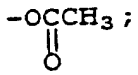
C



wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

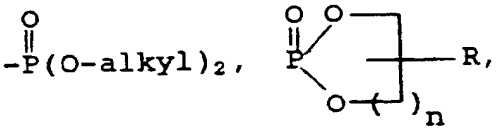


R_2 is hydrogen, hydroxy,



R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,



halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

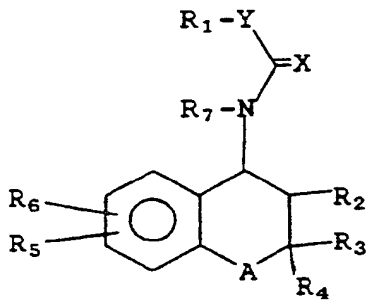
R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 and R_8 are each independently selected from hydrogen, alkyl, alkenyl, aryl, (heterocyclo)alkyl, heterocyclo, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R_7 and R_8 taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphilinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and

n is 1, 2 or 3;

E

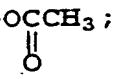


wherein A can be $-CH_2-$, -O-, $-NR_9$, -S-, -SO- or $-SO_2-$, where R_9 is hydrogen or lower alkyl of 1 to 4 carbons;

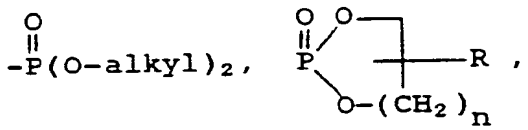
wherein X is oxygen or sulfur;

Y is $-NR_8$, -O-, -S- or

R_1 is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl;
R_2 is hydrogen, hydroxy,

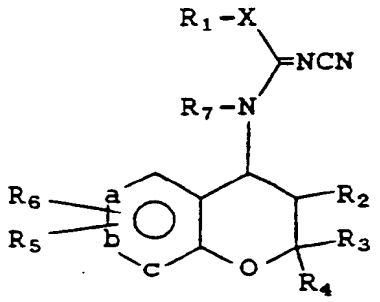


R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;
R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,

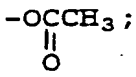


halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;
R_6 is selected from H, alkyl, halo, OH, O-alkyl, amino and substituted amino;
R_7 and R_8 are each independently selected from hydrogen, alkyl, arylalkyl;
n is 1, 2 or 3; and,
R_{10} is hydrogen, hydroxy, alkyl or O-alkyl; and compounds having the general formula

F

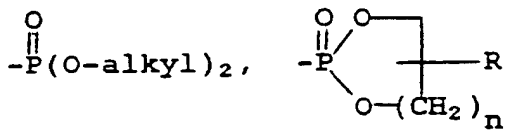


wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;
where X is oxygen or sulfur;
R_1 is selected from aryl, arylalkyl, (heterocyclo)alkyl, heterocyclo, cycloalkyl and (cycloalkyl)alkyl.
R_2 is hydrogen, hydroxy,



R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;
R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN,

$-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,



halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 is selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and,

n is 1, 2 or 3.

Claims for the following Contracting State : ES

1. A method for the preparation of a pharmaceutical composition useful in protecting an organ and surrounding cells in a mammalian species subject to an organ surgery procedure which comprises combining a potassium channel activator with a pharmaceutically acceptable carrier.

2. The method of claim 1 wherein said procedure is cardiopulmonary bypass surgery.

3. The method of claim 1 wherein said procedure is organ transplant surgery.

4. The method of claim 3 wherein said procedure is heart transplant surgery.

5. The method of claim 1 wherein the pharmaceutical composition prepared is added to a solution used in said procedure in order to preserve, protect or maintain organ function.

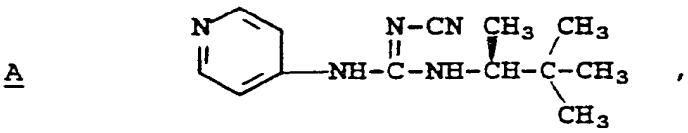
6. The method of claim 5 wherein the pharmaceutical composition prepared is added to a cardioplegic solution used to arrest, perfuse, store and/or protect a heart involved in a cardiopulmonary bypass or heart transplant procedure.

7. The method of claim 2 wherein the pharmaceutical composition prepared is administered to a mammalian specie undergoing said bypass procedure before and/or during and/or aftr said procedure.

8. The method of claim 4 wherein the pharmaceutical composition prepared is administered to an organ donor before, during or after removal of said organ from said donor.

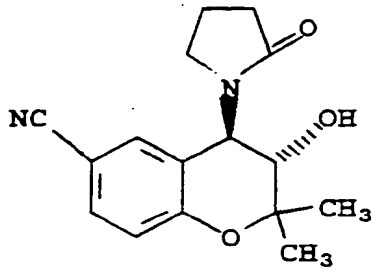
9. The method of claim 4 wherein the pharmaceutical composition prepared is administered to an organ recipient before, during or after transplantation of said organ into said recipient.

10. The method of any of claims 1 to 9 wherein said potassium channel activator is selected from



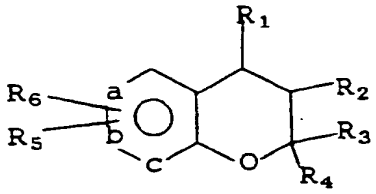
known as pinacidil; the compound

B



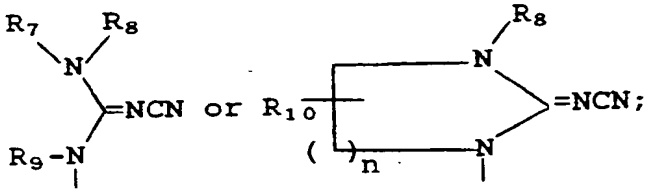
known as cromakalim; nicorandil; minoxidil; compounds having the formula

C

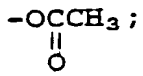


wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

R_1 is

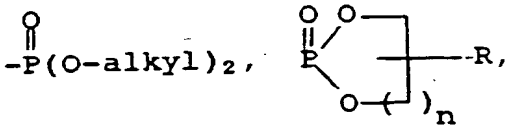


R_2 is hydrogen, hydroxy,



R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,



halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 and R_8 are each independently selected from hydrogen, alkyl, alkenyl, aryl, (heterocyclo)alkyl, heterocyclo, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R_7 and R_8 taken together with the nitrogen atom to which

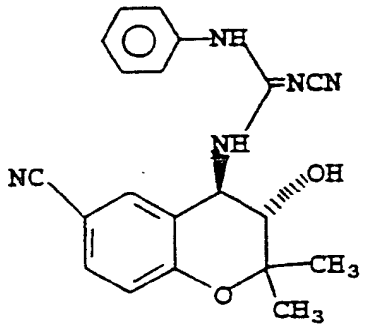
they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphilinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and

n is 1, 2 or 3;

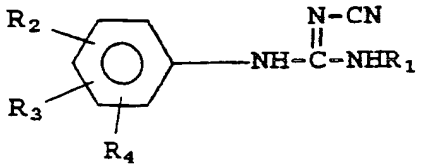
with the compound

C'

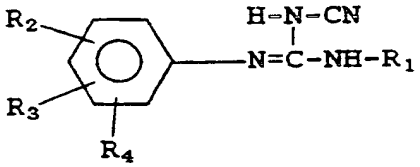


being preferred; compounds having the formula

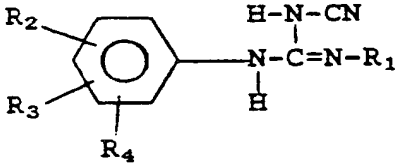
D



and its possible tautomers



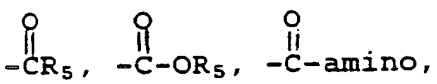
and



including pharmaceutically acceptable salts;

wherein R_1 is alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, arylalkyl or cycloalkylalkyl;

R_2 is -C≡N, $-NO_2$,



$$-\overset{\overset{O}{\|}}{C}\text{-substituted amino,}$$

$-CF_3$ or

$$-S-R_1;$$

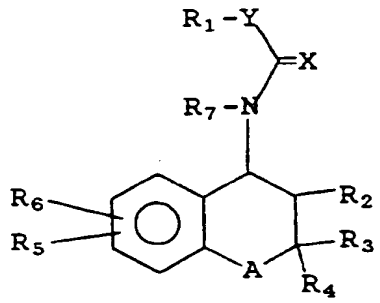
R_3 and R_4 are each independently selected from $-R_2$, hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, halo, alkoxy, -NHalkyl, -N-(alkyl)$_2$, -S-alkyl, -O-arylalkyl, -S-arylalkyl or -S-aryl, -O-aryl, -NHarylalkyl, or R_2 and R_3 taken together are a group which forms a ring with the two carbon atoms to which they are attached, which group is selected from

$$-S-(CH_2)_n-CH_2-,$$

$$-CX(CH_2)_pCH_2-, \quad -C-CH_2(CH_2)_pX-;$$

wherein
m = 1 or 2,
n = 3-5,
p = 2-4,
X is 0, NR_5, CH_2; and
R_5 is hydrogen or R_1;
compounds having the general formula

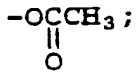
E



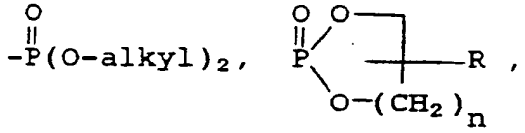
wherein A can be $-CH_2-$, -O-, $-NR_9-$, -S-, -SO- or $-SO_2-$, where R_9 is hydrogen or lower alkyl of 1 to 4 carbons;
wherein X is oxygen or sulfur;
Y is $-NR_8$, -O-, -S- or

$$-\overset{R_{10}}{\underset{|}{C}}H-;$$

R_1 is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl;
R_2 is hydrogen, hydroxy,

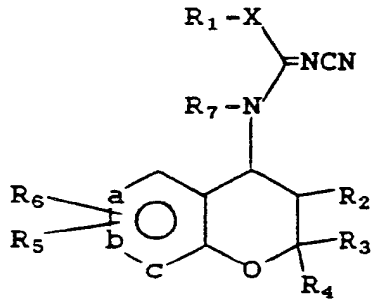


R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;
R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,

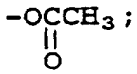


halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;
R_6 is selected from H, alkyl, halo, OH, O-alkyl, amino and substituted amino;
R_7 and R_8 are each independently selected from hydrogen, alkyl, arylalkyl;
n is 1, 2 or 3; and,
R_{10} is hydrogen, hydroxy, alkyl or O-alkyl; and compounds having the general formula

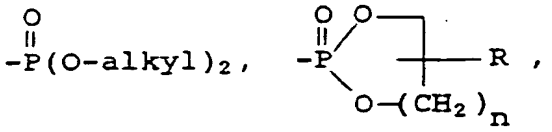
F



wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;
where X is oxygen or sulfur;
R_1 is selected from aryl, arylalkyl, (heterocyclo)alkyl, heterocyclo, cycloalkyl and (cycloalkyl)alkyl.
R_2 is hydrogen, hydroxy,



R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;
R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,



halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

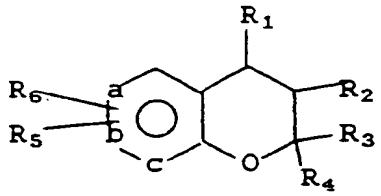
R_7 is selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and,

n is 1, 2 or 3.

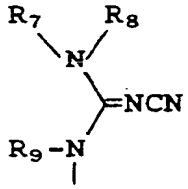
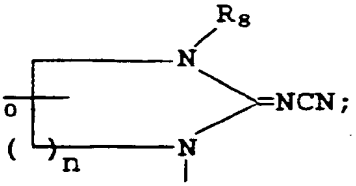
11. The method of any of claims 1 to 10 wherein said potassium channel activator shows little or no vasodilation activity in normal tissue.

12. The method of claim 11 wherein said potassium channel activator is selected from

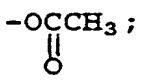
C



wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;

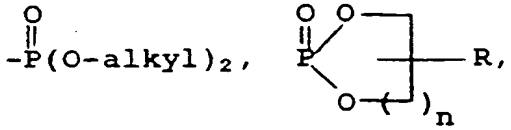
R_1 is  or  ;

R_2 is hydrogen, hydroxy,



R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,



halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl

and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

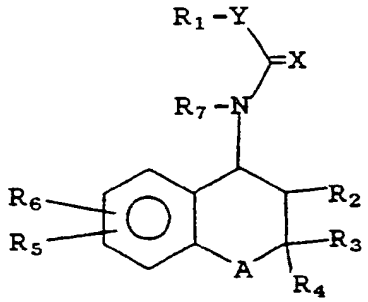
R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;

R_7 and R_8 are each independently selected from hydrogen, alkyl, alkenyl, aryl, (heterocyclo)alkyl, heterocyclo, arylalkyl, cycloalkyl and (cycloalkyl)alkyl, substituted alkyl wherein the substituents include alkoxy, alkylthio and substituted amino, or R_7 and R_8 taken together with the nitrogen atom to which they are attached form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorphilinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl or 4-arylalkyl-1-piperazinyl, wherein each of the so-formed groups can be substituted with alkyl, alkoxy, alkylthio, halogen or trifluoromethyl;

R_9 and R_{10} are selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and

n is 1, 2 or 3;

E



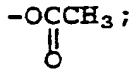
wherein A can be $-CH_2-$, -O-, NR_9-, -S-, -SO- or $-SO_2-$, where R_9 is hydrogen or lower alkyl of 1 to 4 carbons;

wherein X is oxygen or sulfur;

Y is $-NR_8$, -O-, -S- or

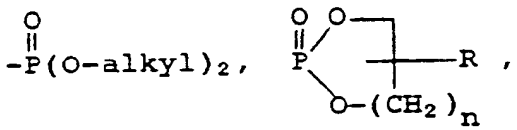
R_1 is aryl, arylalkyl, heterocyclo or (heterocyclo)alkyl;

R_2 is hydrogen, hydroxy,



R_3 and R_4 are each independently hydrogen, alkyl or arylalkyl, or, R_3 and R_4 taken together with the carbon atom to which they are attached form a 5- to 7-membered carbocyclic ring;

R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,

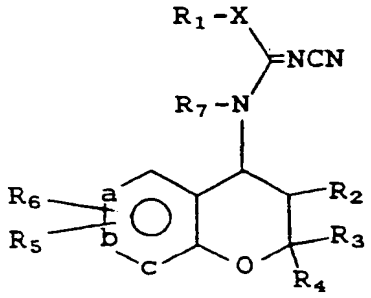


halogen, amino, substituted amino, O-alkyl, OCF_3, OCH_2CF_3, -OCOalkyl, -OCONRalkyl, -NRCOalkyl and NRCOOalkyl, $NRCONR_2$ wherein R in each of the above groups can be hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or (cycloalkyl)alkyl;

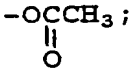
R_6 is selected from H, alkyl, halo, OH, O-alkyl, amino and substituted amino;

R_7 and R_8 are each independently selected from hydrogen, alkyl, arylalkyl;
n is 1, 2 or 3; and,
R_{10} is hydrogen, hydroxy, alkyl or O-alkyl; and compounds having the general formula

F



wherein a, b, and c are all carbons or one of a, b and c can be nitrogen or -NO- and the others are carbons;
where X is oxygen or sulfur;
R_1 is selected from aryl, arylalkyl, (heterocyclo)alkyl, heterocyclo, cycloalkyl and (cycloalkyl)alkyl.
R_2 is hydrogen, hydroxy,



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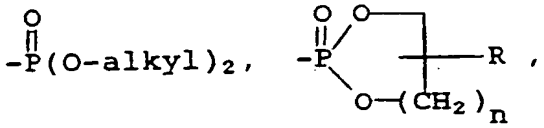
R_5 is selected from H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl, -CN, $-NO_2$, -COR, -COOR, -CONHR, $-CONR_2$, $-CF_3$, S-alkyl, -SOalkyl, $-SO_2$alkyl,



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R_6 is selected from H, alkyl, OH, O-alkyl, amino, substituted amino, CN, and NO_2;
R_7 is selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl or cycloalkylalkyl; and,
n is 1, 2 or 3.

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European Patent Office
Office européen des brevets

(11) Publication number: **0 480 257 A3**

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(51) Int. Cl.[5]: **A61K 31/35**, A61K 31/40

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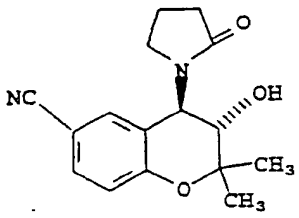
W-8000 München 86(DE)

(54) Use of a potassium channel activator for pharmaceutical compositions useful in cardiopulmonary bypass and organ transplant.

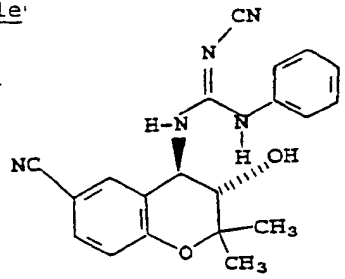
(57) In accordance with the present invention novel methods for cardiopulmonary bypass and organ transplant, each employing a potassium channel activator, are disclosed. The use of a potassium channel activator has been found to reduce the damage or ischemia induced by the bypass and transplant procedures.

EP 0 480 257 A3

Compounds Tested in the Example



Cromakalim



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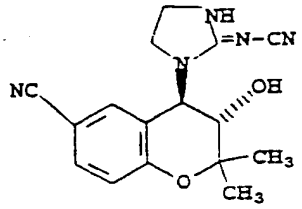

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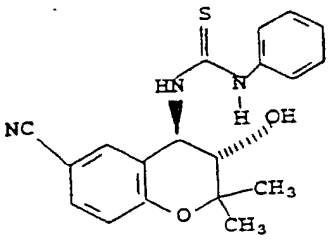
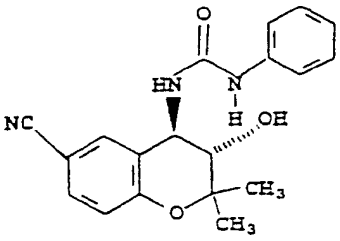


E'



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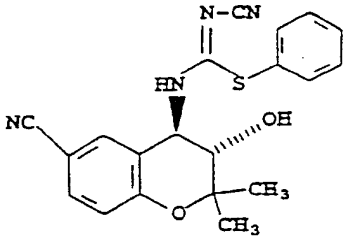

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European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number

EP 91 11 6486

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 351 767 (SUIBB) * Page 2; example 5; claims *	1,5,10	A 61 K 31/35 A 61 K 31/40
P,X	EP-A-0 401 010 (SQUIBB) * Claims; pages 10,11 *	1,10-12	
X	EP-A-0 354 553 (SQUIBB) * Page 2; example 33; claims *	1,10	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely :

Claims searched incompletely : 10-12

Claims not searched :

Reason for the limitation of the search:

The markush formulas of claim 10 allow for far too many possible compounds to be economically searcheable, so the search has been limited to the examples/preferred compounds; only structure D has been fully searched.

Place of search	Date of completion of the search	Examiner
THE HAGUE	08-05-1992	KLAVER T.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0407)

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,

namely claims:

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,
namely:

See sheet -B-

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid.

namely claims:

☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.

namely claims:

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims 1-9,10 in part, 11: Use of pinacidil as a potassium channel activator in surgery.
2. claim 10 in part : Use of cromakalim as such.
3. claim 10 in part : Use of nicorandil as such.
4. claim 10 in part : Use of minoxidil as such.
5. claims 10 & 12 in part: Use of compounds of formula C as such.
6. claim 10 in part : Use of compounds of formula C' as such.
7. claim 10 in part : Use of compounds of formula D as such.
8. claims 10 & 12 in part: Use of compounds of formula E as such.
9. claims 10 & 12 in part: Use of compounds of formula F as such.